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HIGH PRODUCTION VOLUME (HPV) CHEMICAL CHALLENGE PROGRAM

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FINAL SUBMISSION

For

Phenol, 2-(1-methylpropyl)-4, 6-dinitro-

CAS No. 88-85-7

Submitted to the US EPA

BY

Chemtura (formerly Crompton) Corporation

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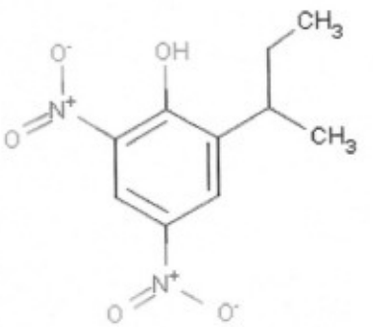
1. General Information

1.1 CAS Number: 88-85-7

1.2 Molecular Weight: 240.2

1.3 Structure and formula: $C_{10}H_{12}N_2O_5$



1.4 Introduction

Phenol, 2-(1-methylpropyl)-4,6-dinitro- (DNBP; Dinoseb) is used as a polymerization inhibitor for the production of styrene. Prior to 1990, DNBP was also used as a pre-emergence herbicide. Based on its toxicity, the use of DNBP as a herbicide is limited to certain government approved agricultural commodities.

2. Review of Data

Chemtura Corporation has undertaken a comprehensive evaluation of all relevant data on the SIDS endpoints of concern for DNBP.

The availability of the data on the specific SIDS endpoints is summarized in Table 1.

Table 1: Available adequate data on Phenol, 2-(1-methylpropyl)-4,6-dinitro-

CAS NO. 88-85-7	Information Available?	GLP	OECD Study?	Other Study?	Estimation Method?	Acceptable?	SIDS Testing Required?
	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
Physicochemical							
Melting Point	Y					Y	N
Boiling Point	Y					Y	N
Vapour Pressure	Y					Y	N
Water Solubility	Y					Y	N

Partition Coefficient (Kow)	Y					Y	N
Environmental Fate							
Biodegradation	Y	Y	Y		Y	Y	N
Hydrolysis	Y			Y		Y	N
Photodegradation	Y				Y	Y	N
Transport and Distribution between Environmental Compartments	Y				Y	Y	N
Ecotoxicology							
Acute Fish	Y	N	N	Y	N	Y	N
Acute Daphnia	Y	N	N	Y	N	Y	N
Acute Algae	Y	Y	Y	N	N	Y	N
Toxicology							
Acute Oral	Y	Y	N	Y	N	Y	N
Repeat Dose toxicity	Y	N	N	N	N	Y	N
Genetic toxicity – Gene mutation	Y	N	N			Y	N
Genetic toxicity – Chromosome Aberration	Y	Y	Y			Y	N
Reproductive toxicity	Y	N	N	N	N	Y	N
Developmental toxicity/teratogenicity	Y	N	N	Y/N	N	Y	N

A. Evaluation of Physiochemical Data

1. Melting Point

   The melting point is quoted as 38-42°C in a peer-reviewed publication.

2. Boiling Point

   The boiling point is quoted as 332°C in the EXTOXNET database.

3. Vapour Pressure

   Values for vapor pressure quoted in the literature range between 2.3E-5 hPa and 7.0E-5 hPa at 30 – 20°C, respectively.

4. Water Solubility

   The water solubility is quoted as 52 mg/L at 25°C in a peer reviewed publication.

5. Partition Coefficient

   The Log Pow is quoted as 3.56 in a peer-reviewed publication.

Summary of Physicochemical Properties Testing: Existing data for melting point, boiling point, vapour pressure, partition coefficient and water solubility are considered to fill these endpoints adequately.

B. Evaluation of Environmental Fate Data

1. Biodegradation

The biodegradability of the chemical has been determined following OECD 301B. Based on the pass levels (60% in a 10-d window), the test item was considered as non-biodegradable.

2. Hydrolysis

A peer-reviewed report in the literature shows DNBP to be stable in aqueous solution over the pH range of 5-9.

3. Photodegradation

The potential for photodegradation of DNBP has been estimated using the AOPWIN v1.90, and indicated atmospheric oxidation via OH radicals reaction with a half-life of 31.8 hours.

4. Transport and Distribution between Environmental Compartments

An Epiwin Level III Fugacity Model calculation has been conducted for DNBP and indicates distribution mainly to soil and, to a lesser extent, water for emissions of 1000 kg/hr simultaneously to air water and soil compartments.

Summary of Environmental Fate Testing: Existing data for photodegradation, hydrolysis, biodegradation and transport and distribution between environmental compartments are considered to fill these endpoints adequately.

C. Evaluation of Ecotoxicity Data

1. Acute Toxicity to Fish

DNBP has been shown to be toxic to fish in several studies reported in the peer-reviewed literature (LC50 = 0.08 -0.7 mg/L).

2. Acute Toxicity to Algae

In an OECD TG 201 algal study, the test item was tested at .030, .081, .219, .590 and 1.594 mg/L along with negative and positive controls. The cell growth was measured at 24, 48 and 72 hours after initiation of the test. The 72 hour values were:

EbC50 = .21 mg/L

ErC50 = .74 mg/L

NOEC = .030 mg/L

LOEC = .081 mg/L

DNBP has been shown to be toxic to algae (EC 50 = 4.3 - > 10 PM) in a study reported in the literature.

3. Acute Toxicity to Daphnia

DNBP has been shown to be toxic to daphnia (EC50 = 0.24 mg/L) in a peer-reviewed study reported in the literature.

4. Acute Toxicity to Bacteria (non-SIDS endpoint)

A value of EC50 > 6.4 mg/L is reported in the literature for this non-SIDS endpoint.

5. Chronic Toxicity to Fish (non-SIDS endpoint)

The $NOEC_{(weight)}$ for chronic effects on development and growth of fry in this study was < 0.5 pg/L. The concentration not affecting survival of the fry was between 4.9 and 10 ug/L.

Summary of Ecotoxicity Testing: DNBP is toxic to the aquatic environment. All SIDS endpoints have been filled adequately.

D. Evaluation of Human Health Effects Data

1. Acute Oral Toxicity

The acute oral toxicity of a formulation containing DNBP has been examined in two studies conducted to GLP and following EPA OPP guidelines. In these studies the LD_{50} (rat) values ranged from 54.7 to 103.7 mg/kg bw.

2. Acute Inhalation Toxicity (non-SIDS endpoint)

In two GLP studies conducted to EPA OPP guidelines, the acute inhalation toxicity to rats of a formulation containing DNBP was found to be between 0.033 and 0.29 mg/L (based on the active).

3. Acute Dermal Toxicity (non-SIDS endpoint)

In two GLP studies conducted using methods similar to EPA OPP guidelines, the acute dermal toxicity to rabbits of a formulation containing DNBP was found to be between 40 and 146 mg/kg bw.

4. Acute I.P. Toxicity (non-SIDS endpoint)

An LD_{50} (mouse) of 14.1 - 20.2 mg/kg is reported in the literature.

5. Eye Irritation (non-SIDS endpoint)

Formulations containing DNBP were highly irritating to the eyes of rabbits in two GLP studies performed to EPA OPP guidelines.

6. Repeat Dose Toxicity

In a combination subchronic feeding and single generation reproduction study, rats were fed DNBP for a total of 153 days at doses up to 500 ppm. The test groups dosed at 300 ppm and higher were terminated at 21 days due to mortality. In the remaining groups, growth was depressed monotonically. Blood alkaline phosphatase, alanine aminotransferase, potassium and BUN were significantly increased, while LDH and cholinesterase were depressed. Residue levels were dose dependent with blood > feces >urine > adipose >brain > liver. Aminopyrine N-demethylase activity was increased. Organ weights were decreased, while the organ weight/body weight ratios increased. A significant pathological change was diffuse tubular atrophy of the testes, particularly at 200 ppm.

Although only an abstract of the study is available in the literature, it is believed there is sufficient detail available to allow an assessment of repeated dose toxicity and no further studies are proposed to fulfill this endpoint.

7. Genotoxicity

DNBP tested negative in a number of Ames tests using Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA 100 and Escherichia coli strain WP2 uvrA-, both with and without metabolic activation (Arochlor-induced rat liver S9).

DNBP tested positive in an E. coli polA differential toxicity assay (E. coli strains p3478 & W3110) and in a S. typhimurium differential toxicity assay (S. typhimurium strains SL4700, SL4525, TA1978 and TA1538), both test conducted without metabolic activation. It also tested positive in a Bacillus subtilis recombination assay (B. subtilis strains M45 & H17) without metabolic activation, but was negative in a yeast gene mutation assay (S. cerevisiae D3) and in a UDS assay (Human Lung Fibroblast cells, strain WI-38) with and without metabolic activation.

In an OECD TG 473 study, one trial each, in the presence and absence of metabolic activation, was conducted. CHO cells were exposed to the test item in quadruplicate for 3 hours. The test item was positive in this assay.

In an in vivo Drosophila SLRL test using D. melanogaster, DNBP tested

negative when administered to male fruit flies by oral feed.

8. Reproductive and Developmental Toxicity

In a one-generation fertility study DNBP was administered by oral feed to male Sherman rats for up to 77 days. At toxic dose levels the effects upon male reproduction are severe and appear dose related. At toxic dose levels histopathological changes in the gonads are observed that persist following withdrawal of treatment. The extent of the reproductive effects was seen to be beyond what was a consequence of dietary restriction alone. A NOEL of 3.8 mg/kg/day was established for both adult toxicity and reproductive effects, but the extent of the findings suggests that the effects on reproduction are not a consequence of a general systemic toxicity.

There are a number of developmental toxicity studies reported in the literature. In one study, the evaluation of postnatal offspring development following prenatal exposure was examined. Irrespective of the route of administration, the test material was shown to be a developmental toxicant at dose levels that were toxic to the adult. The effects were either embryolethality/embryotoxicity, teratogenicity, fetotoxicity or a combination of effects.

The nature of the findings suggest that developmental toxicity was not a consequence of toxicity to the adult. Some species variation in response was observed, but this was influenced by study design. In a study performed on rabbits following EPA guidelines, a NOEL for maternal and developmental toxicity of 1 mg/kg/day was established.

Summary of Human Health Effects Testing: All endpoints are considered to have been filled adequately.

3. Evaluation of Data for Quality and Acceptability

The collected data were reviewed for quality and acceptability following the general US EPA guidance [2] and the systematic approach described by Klimisch et al [3]. These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. This scoring system was only applied to ecotoxicology and human health endpoint studies per EPA recommendation [4]. The codification described by Klimisch specifies four categories of reliability for describing data adequacy. These are:

(1) Reliable without restriction: Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.

(2) Reliable with Restrictions: Includes studies or data in which test parameters

are documented but vary slightly from testing guidelines.

(3) Not Reliable: Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.

(4) Not Assignable: Includes studies or data in which insufficient detail is reported to assign a rating, e.g. listed in abstracts or secondary literature.

4. Conclusion

Chemtura Corporation has met its commitment for the sponsorship of Phenol, 2-(1-methylpropyl)-4,6-dinitro- under the US EPA HPV Challenge Program.

5. References

[1] US EPA, EPI Suite Software, 2000

[2] USEPA (1998). Guidance for Meeting the SIDS Requirements (The SIDS Guide). Guidance for the HPV Challenge Program. Dated 1 l/2/98.

[3] Klimisch, H.-J., et al (1997). A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. Regul. Toxicol. Pharmacol. 25: l-5

[4] USEPA (1999). Determining the Adequacy of Existing Data. Guidance for the HPV Challenge Program. Draft dated 2/10/99.